Chapter 11
The Duties of Clinical Researchers

A clinical investigator involved in a clinical trial is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan and the applicable regulations; for protecting the rights, safety and welfare of subjects under the investigator's care; and for the control of drugs under investigation. The clinical investigator must also meet the requirements set out by the FDA, European Medicines Agency (EMA) or other regulatory bodies. The qualifications must be outlined in a current resume and readily available for auditors [1].

Clinical investigators face challenges during the conduct of clinical trials that are distinctly different from those encountered during the routine practice of medicine. Many of these challenges stem from regulatory requirements, the Guidelines for Good Clinical Practice (GCP) and the rigorous nature of clinical trials. When conducting a clinical trial, it is important that clinical investigators successfully meet all research expectations [2]. A clinical investigator's primary responsibility is to conduct research that contributes to generalisable knowledge while protecting the rights and welfare of human participants [3].

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11.1 Conducting Ethical Research

It is important to conduct research in an ethical manner. Investigators must be diligent throughout all stages while conducting a clinical trial, which include the steps of designing the protocol and deciding which trials to conduct, as well as during the performance of the study and after the conclusion of the study. Although there are multiple regulatory safeguards designed to ensure the ethical conduct of research, it is ultimately the investigator's responsibility to ensure that the research is fair and equitable to study participants. When the investigator is also the sponsor of the study, then responsibilities also include protocol design [3].

The majority of investigators respect the importance of conducting ethical research, but even the most cognisant investigators may encounter unexpected challenges. For example, an ethical dilemma can arise when the control arm of a trial does not correlate with the standard treatment typically prescribed by the physician. Issues like this need to be discussed during trial design and considered as part of the decision to implement new trials at the site. Clinical investigators need to review the protocol in detail and understand the primary end point of every study they oversee. This practice prevents inadvertent issues arising that can affect patient safety and/or the scientific integrity of the study. For example, if a study is designed to provide adjuvant treatment to patients, but the investigator is slow to identify the first signs of relapse, then the quality of the science suffers and can, potentially, affect approval of the agent by the FDA. Understanding the research protocol and investigator's brochure [4] helps to prevent potential issues [3].

11.2 Informed Consent Process

Informed consent is a process that extends beyond a patient simply signing a consent form. Clinical research requires that individuals be fully informed about the study they are being offered.

Throughout the informedconsent process, potential research participants should be given the opportunity to learn about the research study and have all their questions answered.

According to the Belmont Report [3], individuals must be given the opportunity to make informed choices with regard to how they will be treated and what interventions they will participate in. Potential participants should be informed about the risks, anticipated benefits and any alternative treatment options they have, including hospice care. An appropriate informed consent process needs to be conducted by a qualified individual who understands the clinical trial protocol and has knowledge about the potential benefits and adverse effects of the therapeutic agent under investigation [3].

If the investigation is a randomised, controlled clinical trial, research staff must alert potential participants to the concept of randomisation. The potential participant must also be informed about the treatment that will be given to individuals who are randomly assigned to the control arm of the trial. They should be told that neither they nor their provider can control which arm of the trial they are randomised to. Patient-oriented educational materials about clinical trials are available, free of charge, on ASCO's patient education website,www.cancer.net [5].

11.3 Statement of Investigator

In the USA, when conducting clinical research with an investigational agent, such as a drug or a biologic, an investigator must comply with all applicable FDA rules and regulations. An investigator must also complete the Statement of Investigator (FDA Form 1572) before participating in an FDA-regulated investigation [6]. FDA Form 1572 is a legally binding document designed to inform clinical investigators of their research obligations and secure the investigators' commitment to follow pertinent FDA regulations. By signing this form, the investigator confirms that they will abide by all FDA regulations [3].

11.4 Reporting Adverse Events

It is required to document all AEs that occur during the course of a clinical investigation. Keeping a log of AEs is a helpful organisational tool, and such logs should be reviewed during regularly scheduled research team meetings. It is important that a principal investigator be aware of AEs because an event may trigger the need for a dose adjustment. Serious or unanticipated events should be addressed immediately and may require meeting outside regularly scheduled team meetings [3].

11.5 Maintaining Accurate Records

The importance of maintaining accurate records when conducting clinical research cannot be overstated. It is important that all collected data match the information found in source documents, such as a pathology report or the patient's medical record. In addition, issues such as protocol deviations must be well documented. A situation that occurs today may not be reviewed or questioned until months or years in the future. It is almost impossible to recall particular study conduct events during an audit unless they have been well documented [3].

As with many investigator responsibilities, an investigator is permitted to delegate tasks associated with data collection and documentation to a qualified individual. However, it is important that the investigator knows that this individual will appropriately conduct the delegated tasks. One way to ensure clear communication between an investigator and staff is to use a delegation log, which is a signed record of which study tasks have been assigned to which individual. It is important that the investigator be available to the staff to answer questions and make decisions [3].

11.6 Steps to Becoming a Clinical Trial Investigator

Being involved in clinical trials enables physicians to learn, become exposed to new medical therapies and provide additional options or alternative treatments for their patients. The following steps are an overview of the process for professionals interested in conducting clinical trials [7]:

1. *Learn about regulations.* Before becoming involved in clinical research, physicians should have a thorough understanding of the various regulations related to the field. That will help them to ensure that their study sites are in, and remain in, compliance. In the USA, physicians conducting clinical trials should be familiar with parts *50*, *54*, *56* and *312* of the Code of Federal Regulations (CFR) Title 21. These regulations define what is required by the US FDA. Other countries have their own requirements.

   Those who want to conduct trials should know about GCP, which refers to the principles and processes investigators are expected to follow. Compliance with GCP ensures that the rights, well-being and confidentiality of study subjects are protected. It also assures the collection of reliable data for submissions to regulatory agencies.
2. *Establish the needed infrastructure.* Many physicians plan to integrate clinical research space into their existing practices. To accommodate the conduct of clinical trials, they have to think about drug storage, archive space and equipment, as well as providing workspace for clinical research associates.

   Also, the practice will need a clinical research coordinator, who will handle the management and documentation of the trial.
3. *Search for clinical trials.* Many physicians browse helpful websites, such as CenterWatch.com and ClinicalTrials.gov,

while others contact drug companies whose products they prescribe. A physician can also submit his or her contact information into an online database of potential investigators. Many contract research organisations (CROs), including PPD (define acronym, or, better, replace with full term as this acronym does not appear again), recruit clinical trial investigators this way.

4. *Complete needed forms.* Once a physician has been identified as a potential investigator, he or she is required to complete several forms. These forms are required documentation needed to register the physician as a clinical trial investigator and to track and evaluate the ethical and procedural conduct of trials.

   Required documents for an IND trial in the USA include a confidential disclosure agreement; Form FDA 1572; a protocol, amendment and signature page; an investigational drug brochure; curriculum vitae for the principal investigator and sub-investigators; an IRB/IEC approval letter and roster; laboratory certifications and normal ranges; and the principal investigator's financial disclosure statement.
5. *Prepare for a pre-study visit.* As part of the qualification process for a newly awarded study, each potential study site will be visited by a CRA to evaluate the investigator's experience, expertise and interest, as well as his or her staff, facility and potential patient population available for the trial. This visit is called a pre-study site visit. There are also several other items the CRA might want to discuss during the visit, including whether the physician is engaged in competing studies at the same time.
6. *Receive IRB approval.* An IRB or an IEC is a group designated to protect the rights, safety and well-being of patients involved in a clinical trial. They do that by reviewing all aspects of the trial and approving its startup. An IRB or IEC must give approval before any clinical trial can begin and then keep close tabs on the progress of the research.

7. *Sign the contract.* Before the clinical trial starts, the investigator and the sponsor or a CRO needs to sign a contract. This usually lists the investigator's responsibilities, including the number of subjects he or she is expected to enrol, timelines for enrolment and the regulatory requirements. It also includes the sponsor's responsibilities.
8. *Get Ready for a site initiation visit.* A CRA will conduct a site initiation visit after the IRB or IEC has given its approval, and the contract and all essential documents have been completed. The purpose of this visit is to ensure that everything is in place for the investigator to begin enrolling patients.
9. *Enrol first patients.* An investigator or his or her staff is normally responsible for recruiting patients, scheduling their visits, retaining them and making sure they are compliant with the protocol throughout the trial.
10. *Take advantage of the opportunity.* A clinical investigator's role is crucial in the development and advancement of drugs, therapies and medical devices. However, investigators also gain multiple advantages, including the opportunity to learn new skills and explore new challenges.

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